Air Pollution and Its Effect on Health

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• *An experimental study of the effect of air pollutants on health can be undertaken only subsequent to the creation of synthetically polluted atmosphere in exposure chambers as a readily available and easily controllable laboratory tool. The many and varied pollutants must be studied singly and in combination so as to reproduce any synergistic or antagonistic effects that may exist. A study of pollutant substances at their source is wholly inadequate in view of the pronounced photo-chemical activity in the atmosphere. The products of this activity may well be the significant ones insofar as morbid effects are concerned.*

In the acute and subacute biological studies, both in vitro and in vivo systems are being used with the experimental progression being from the simple to the complex.

A PRESENTATION of the effects of air pollutants on health may be compared with a discussion of the effects of microorganisms on health; the agents concerned with both are apparently limitless. The many and varied atmospheric pollutants, their ubiquity, their ever-changing status in a physically and chemically dynamic atmosphere, and the variations in human response unite to make a study of their biological effects extremely difficult. Clinically, this is so even during transient disaster periods when pollutant concentrations are high, the emission sources are limited, and epidemiological surveys can be undertaken. Studies initiated at a time when epidemiologic efforts have proven valueless and when pollutant levels are below the threshold for the production of immediate clinical symptoms would appear to be well-nigh impossible of success. Experimental investigations appear equally difficult. A fundamental requirement for a research program of this type is the exact duplication of atmospheric pollutants in a readily available and easily controllable laboratory tool form. Only within the recent past have studies in this direction been successful. On both the clinical and the experimental levels, physiologic and pathologic studies fall far short of satisfaction because of the nonspecific and quite subtle changes that occur in response to pollutant exposure.

Historically, clamor and concern over air pollution have followed episodes in which geographic, meteorologic and industrial factors have united to produce transient intervals of high pollutant concentration characterized by severe symptoms affecting a significant percentage of the exposed population. Deaths have occurred in a smaller but still significant number of exposed residents.

Six acute episodes have now been recorded, two in the Meuse Valley, Belgium, in 1915 and 1930, respectively; two in Donora in the years 1945 and 1948; one in Poza Rica, Mexico, in 1950; and, the most recent, the great London fog of early December 1952. Sufficient data are available to make at least a partial critical study of four of these episodes: the 1930 Meuse Valley incident,[15] the second Donora episode of 1948,[1, 18] the Poza Rica investigation of 1950[17] and the London fog of 1952.[6, 7] It is of considerable interest, although somewhat disheartening, that the agents responsible for the morbidity and mortality were positively identified in only one of the four—the Poza Rica incident, which was the most limited and restricted of all. In Poza Rica the pollutant was hydrogen sulphide, an asphyxiating gas; the source was a recycling and sulphur-recovery plant; and concentrations of the pollutant were well above the maximum allowable concentration (MAC) of 20 parts per million (ppm). In none of the other incidents could a single pollutant be inculpated as either the only or even a critical toxic agent.

High on the list of suspected agents in the Donora and London episodes were sulphur-bearing compounds expressed as measured sulphur dioxide. Since the MAC of sulphur dioxide is 10 ppm, it is of interest to observe that the concentration of sulphur dioxide in Donora measured at the time the fog was lifting was .5 ppm,[22] and in London on December 7 and 8, 1952, the concentrations measured 1.399 and 1.339 ppm, respectively.[7] In the Meuse Valley episode hydrogen fluoride[16] was suspected as the principal pollutant; concentrations of 0.5 ppm were calculated (not measured) whereas the accepted MAC is 3 ppm. Sulphur dioxide, a subsequent entry into the field of suspicion in the Meuse Valley episode, was estimated to be present up to 8 ppm

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and concentrations of up to 40 ppm were considered as possibilities. There are, of course, no data available to substantiate these latter estimates. It should be quite apparent that since episodes characterized by time limits, restricted geographic locations, specific meteorologic circumstances, and abnormally high pollution concentrations have proven to be beyond exact analytical pinpointing both as to the toxic agents and their morbid effect, similar studies on subtoxicological levels of pollutants must be approached with great caution.

CLASSIFICATION

Pollutants created by man have united with natural geographic and meteorological conditions to produce a polluted atmospheric environment in Southern California of sufficient frequency, duration, and intensity that certain measurable effects on health may properly be anticipated. These effects are in all probability the result of the summation of pollutant activity rather than the direct response to a single pollutant substance. In planning a study of these effects the following questions must be considered. One, what is the physical state of the pollutant material: gaseous, gaseous-particulate (aerosol), solid-particulate (soot), or combinations of these? Two, what is the chemical nature of the pollutants at the time of emission and what new compounds form subsequent to the photochemical activity of the atmosphere? Three, is the health effect related to the physical and chemical nature of the pollutant or do allied factors enter, including, as studied by others, possible increased host susceptibility to upper and lower respiratory tract disease?[2, 24] Four, is the host response specific in terms of specific pollutants? Five, do various pollutants act synergistically or in combination to produce a morbid response since even in disaster the MAC of the toxic substances measured has with one exception never been reached? Six, is the effect solely one of addition of toxic substances to the atmosphere or is there a secondary factor such as interference with solarization, an item related to skin tumor morbidity and antirachitic activity?[3] Finally, is there a psychic effect, and if so, how can it be measured?

The host response to air pollution may arbitrarily be divided into three clinical types: the acute, subacute and chronic. During periods of abnormally high pollutant concentration, immediate clinical effects may be noted, ranging from eye and upper respiratory tract irritation through respiratory embarrassment with dyspnea and chest pain to extreme morbidity with ultimate death. This *entire* spectrum of symptomatology is usually manifest in most of the exposed population group, with the severity of symptoms tending to increase in proportion to the prior cardiorespiratory disability of the exposed persons. The mass effects are transitory and disappear with a decrease in pollutant concentration to tolerated levels. It is of significance that in the Donora and London episodes the most severe illnesses and the greatest number of fatalities occurred in the older age groups and primarily among persons with heart disease, bronchitis, emphysema, bronchial asthma and pulmonary fibrosis. The milder symptoms, usually confined to exposed mucous membrane surfaces of the eyes and upper and lower respiratory tract, are as a rule limited to the healthy young and adult population groups. Retrospective studies following disaster periods indicate that a great many pollutant substances, active in an as yet undetermined cooperative manner, unite to produce the morbid effects described. Studies now going on indicate that specific pollutant host effects are transitory, especially in persons free of preexisting disease.

Subacute effects may be arbitrarily divided on the basis of the individual host under study. In the disease-free members of the exposed population, the subacute effects are characterized by sensory and cardiorespiratory symptoms that are more inconvenient than they are disabling. Lacrimation, rhinorrhea, cough, and occasional headache are all on the minimal clinical level and disappear with the disappearance of the abnormal pollutant concentration. The second type of response is that seen in exposed persons with antecedent cardiorespiratory disease. It would be extremely hazardous not to ascribe some progressive deleterious effect on an already impaired cardiorespiratory system by pollutants present most of the time. Even greater potential danger may threaten persons with marginally or critically decompensated cardiorespiratory systems, for they are conceivably capable of responding to very low concentrations. It is surely this group which is the primary source of deaths during extremely high concentration periods.

Cases of chronic or extremely delayed effect are even more of an arbitrary group than the former two. In effect, all people, without exception, may be responding on this level to the ever-present albeit ever-changing concentrations of atmospheric pollutants. In urban centers the exposure is for the entire life span, and it is this latter observation that must be considered in an assessment of the role of air pollution as one possible etiologic agent responsible for the increasing frequency of lung cancer. Certain epidemiologic observations direct suspicion toward such a relationship: first, the successful demonstration of known cancer-producing substances in the atmosphere and vehicular sources of pollution;[13, 14, 23] second, the experimental production of skin cancer in mice with air-extracted pollutants;[13] third, the reported greater incidence of pulmonary cancer in urban than in rural residents;[12, 21] fourth, the dif-

ferent rates of acceleration of incidence in various localities;[10] fifth, the variations in incidence in the two sexes from country to country;[11] and sixth, and perhaps most significant, is the presence of substances which, although in themselves of questionable carcinogenicity, are considered as providing a mechanism for the biological activity of the known and suspected carcinogens in the atmosphere.[13]

EXPERIMENTAL

The Los Angeles atmosphere, polluted primarily by a hydrocarbon, is characterized chiefly by its pronounced oxidizing capacity.[8] At present the accepted method of measuring pollutant concentration utilizes this chemical observation. Both chemical and biological systems are being used. The former measures total oxidants in the air, and the latter depends on the demonstration of specific morphological changes in certain susceptible botanical species.[4, 9] It seemed proper that in an experimental program to determine the biological effects of atmospheric pollutants in Los Angeles County the oxidation effect should be the first to be studied, particularly in light of the fact that eye irritants have been reported to act on chemical groups common to a number of significant enzymes and enzyme systems. The sulfhydryl group has been demonstrated as the site of the oxidant effect.[5]

The investigational approaches undertaken included (1) protein and enzyme studies to assess pollutant effects on plasma proteins and on enzyme and enzyme systems; (2) respiratory physiology studies utilizing pulmonary function measurements and blood gas analyses; (3) amino acid studies to indicate protein structure changes through the knowledge of the fate of amino acids; (4) hemoglobin studies to determine pollutant effects on oxyhemoglobin and nitric oxide hemoglobin, methemoglobin and sulfhemoglobin formation; (5) pathologic studies to demonstrate morphologic changes in the respiratory tract and other organ systems following pollution exposure and; (6) electrolyte studies to measure changes in blood concentration and electrolyte excretion.

Artificial smog used in this study was prepared according to the method of Shepherd[19] of the National Bureau of Standards and Haagen-Smit of the California Institute of Technology. In the course of analyzing the artificial smog, it became evident that it varied in a manner similar to that of natural smog which changes with the time of day, the geographic location of sample collection, and varying meteorologic conditions. It soon became apparent that the first step would be to carry out a series of repeated determinations so as to observe the entire life cycle of smog from the pollutant source through its build-up and finally to its destruction.

An atmosphere with 4 ppm total oxidant was arbitrarily chosen as the initial exposure concentration. This amount represented ten times the total oxidant, 0.4 ppm, measured in downtown Los Angeles at noon on a smoggy day. Unless otherwise stated, the 4 ppm concentration was used for all studies in this discussion. In instances where neither in vivo nor in vitro changes could be demonstrated at the 4 ppm level, the naturally occurring oxidant level of 0.4 ppm was increased approximately ten thousandfold to 3,000 ppm of oxidant in the atmosphere used for testing. Throughout the entire study it was repeatedly noted that additional tests (which are now being done) would be necessary to further establish the equivalence of natural and synthetic smog.

The biologic studies were planned on the basis of increasing complexity of test systems and all the studies were in the chemical, biochemical, physiologic and pathologic disciplines. The division is one of convenience only, as all studies overlapped. Chemical studies were initially performed for the double purpose of first, determination of smog-sensitive compounds and, second, establishment of the need for air-conditioned laboratories so that the natural atmosphere would introduce no artifact into the data.

Twenty-one amino acids were exposed to 4 ppm of oxidant for 17 hours to measure the changes that occurred. Eight of them—histidine, methionine, tyrosine, tryptophane, lysine, leucune, proline, cystein and glutathione—were found altered. The reaction products were separated from the parent amino acids by filter paper chromatography and detected by the ninhydrin color reaction and, when indicated, by absorption spectroscopy. These studies are as yet incomplete, and the reaction products have not been identified. These experiments are also being undertaken quantitatively.

Investigation of several of the vitamins produced variable results. Vitamin C was not tested, as its instability is well known. Thiamin and pyridoxine were altered by exposure to 4 ppm of smog oxidants for three minutes. Folic acid, carotene and alpha-tocopherol were altered only when exposed to the 3,000 ppm oxidant environment, at which concentration riboflavin and niacin were still unaltered. Cholesterol was oxidized following exposure to the 4 ppm smog for three minutes.

Among the nonprotein hormones it was found that the androgenic, progestational and adrenocortical hormones were destroyed following three minutes of exposure to smog with 4 ppm oxidant. The estrogenic hormones alone withstood all concentrations of smog.

Xanthine and uracil in the purine and pyrimidine group were tested, and alteration could be demonstrated only by exposure to high concentration of

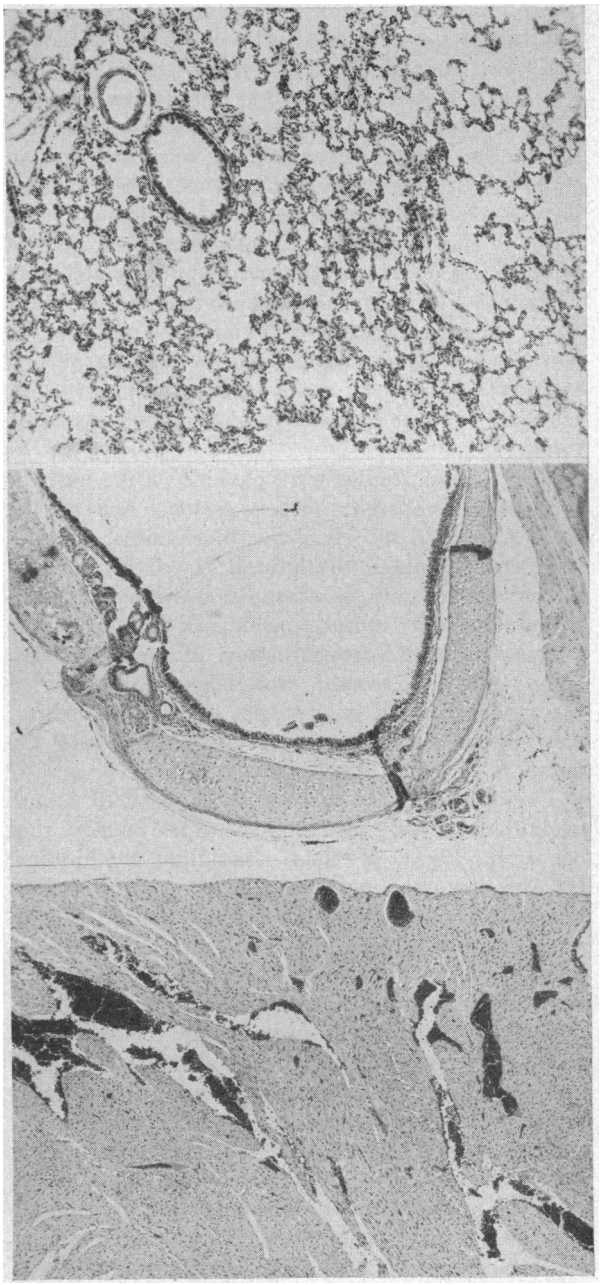

Figure 1.—*Upper:* Lung essentially normal. *Middle:* Trachea shows mild inflammatory response. *Lower:* Myocardium shows intense vascular congestion with focal areas of hemorrhage. (Magnifications × 30.)

3,000 ppm oxidant. In the porphyrin group, cytochrome-C and hemoglobin were significantly altered —30 per cent destruction of the former and 40 per cent methemoglobin formation in the latter. These observations were immediately checked in an in vivo system. Wistar white rats were exposed to smog of 4 ppm oxidant concentration for from 10 to 180 minutes. Hemoglobin oxidation to methemoglobin varied from 0.5 per cent to 10 per cent. In this group of experiments oxides of nitrogen were excluded from the smog mixture so that the oxidant effect could be determined independent of the known nitrogen oxides effect on hemoglobin. Increasing the smog concentration to 3,000 ppm oxidant killed the rats in less than ten minutes. Under these conditions up to 25 per cent methemoglobin was found and the plasma proteins gave altered filter paper electrophoretic patterns with an increase in the gamma globulin fraction.

Enzymatic studies have thus far been limited to the observations of succinic dehydrogenase activity in the liver of normal rats in a medium containing smog oxidants, and in livers of intact animals killed by smog. Data from these studies are as yet incomplete.

Physiological studies on cardiorespiratory activity, using large animal species with and without induced pulmonary disability, have not extended beyond the stage of control determinations of blood gases and the residual content of expired air.

Pathological changes demonstrable by standard histopathological methods proved to be nonspecific following exposure of rats and mice to tenfold the concentration of natural smog. Following a build-up of lethal concentrations to 3,000 ppm oxidant, morphologic findings of respiratory irritation associated with changes of nonspecific asphyxia were noted. Lacrimation and rhinorrhea developed in rats and mice during the build-up of lethal concentrations, as anticipated by the findings of Haagen-Smit. Pollutants were studied singly as well as in atmospheric-occurring combinations. Figure 1 shows the lung, trachea and myocardium of a rat killed by gasoline vapors in an inhalation chamber. Only the myocardium showed changes—pronounced vascular congestion characteristic of asphyxia alone.

The effects of nitrogen oxides on the lung—pronounced vascular congestion, alveolar congestion, hemorrhage and protein exudation into the bronchi, are shown in Figure 2. In Figure 3 are shown changes following exposure to smog with a concentration of 3,000 ppm oxidant. The trachea shows marked inflammation, edema, cellular infiltration and epithelial separation. The lung shows the most intense alveolar and vascular congestion with numerous focal hemorrhages.

To date, acute morphological changes have been significant only in those animals exposed to ten thousand times the concentration of pollutants that exists in Los Angeles atmosphere. Biochemical and chemical changes, however, have been demonstrated following short-term exposure to only tenfold the Los Angeles smog concentration. As yet, a critical appraisal of the acute and subacute data is impossible, as so many of the systems studied have been studied under circumstances that, to say the least, are unphysiologic. Further studies are indicated for an understanding of the mechanisms whereby the

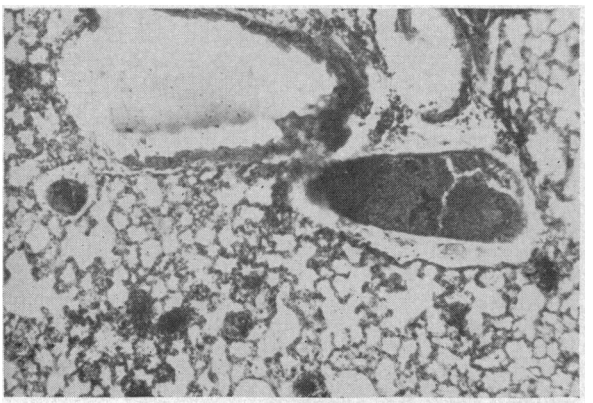

Figure 2.—Lung shows intense vascular congestion. The alveolar septa are engorged, and focal areas of alveolar hemorrhage can be noted. (Magnification × 65.)

TABLE 1.—*Atmospheric samples collected in Los Angeles*

Compound	Amount in mg. Total	Amount in mg. Per 1,000.000 Cubic Feet
Sample 1:		
Pyrene	0.28	0.14
3, 4-benzpyrene	1.84	0.92
1, 12-benzperylene	1.45	1.00
Sample 2:		
Pyrene	0.9	0.32
3, 4-benzpyrene	2.35	0.84
1, 12-benzperylene	0.72	0.35

Sample 1: August 1 to October 15, 1952—42 days actual sampling.

Sample 2: October 21, 1952, to June 1, 1953—59 days actual sampling.

many observed clinical effects are brought about. These include eye irritation, upper respiratory tract and lower respiratory tract irritation, and interference with normal respiratory functions in persons with decreased cardiorespiratory reserve.

The experimental approach to the investigation of the chronic or carcinogenic effect of atmospheric pollutants presents all the difficulties mentioned thus far, plus two critical additional ones. First, there is the necessity for maintaining the animal species for a long time; second, extrapolation of data on carcinogenesis in animals to imply kindred effect in humans is unwarranted.

Initial studies consisted of air sampling for the collection of material for chemical analysis and biological use. In the first series of experiments the collected material was used for skin painting on C57 black mice.

The air sampling revealed the presence of known carcinogenic hydrocarbons in the Los Angeles atmosphere (Table 1).

In addition to the aromatic polycyclic hydrocarbons demonstrated in the atmosphere, the presence of aliphatic hydrocarbons and their oxidation products is offered as being of significance in the pathogenesis of lung cancer in addition to their role as

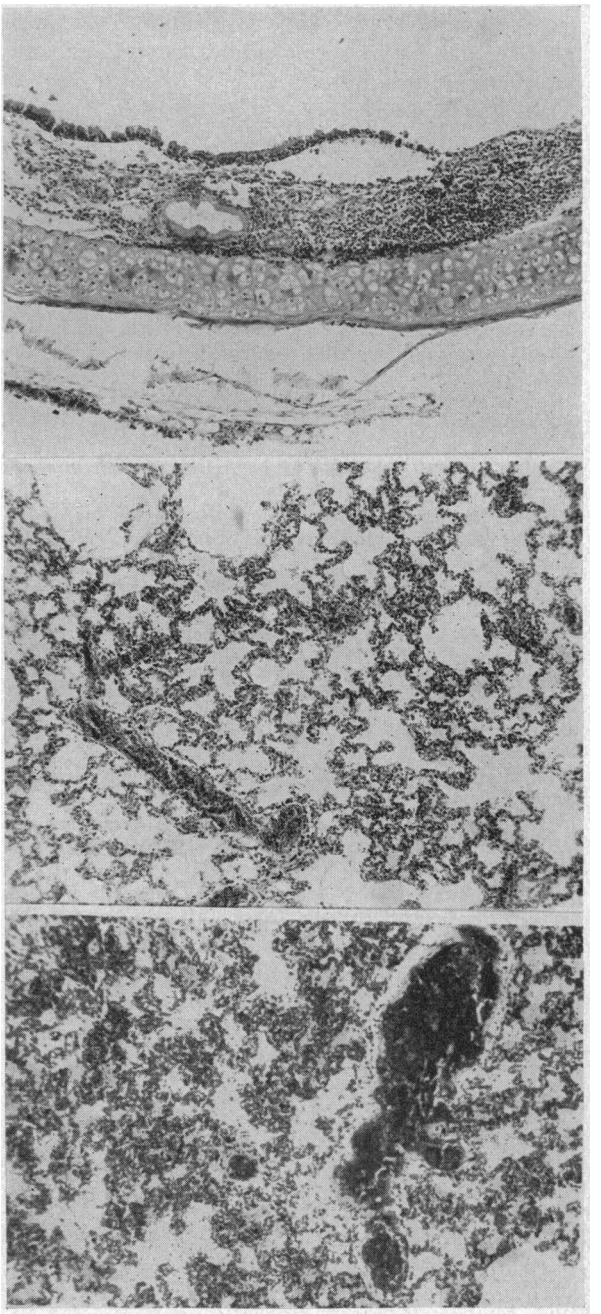

Figure 3.—*Upper:* Subepithelial inflammatory cell infiltration with edema with epithelial separation from underlying cartilage. *Middle:* Diffuse pulmonary congestion with alveolar hemorrhage and inflammatory exudation. *Lower:* Another section from lung showing pulmonary edema. (Magnifications × 65.)

nonspecific irritants. These highly polar substances are important, first, by providing an eluent for the separation of adsorbed carcinogenic hydrocarbon from soot particles in the air and, second, by the formation of various chemical compounds from unsaturated hydrocarbons, including (theoretically) the formation of diepoxides, which have carcino-

genic properties, according to a report on experimental work. Carcinogenic studies using these compounds are in progress.

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